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(57) Abstract

The invention relates to the use of those 5-HT_3 receptor antagonists, which are active in the Rat Model of Colo-rectal Distension at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also migraine.

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MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE

This invention relates to the use of certain compounds which are 5-HT_3 receptor antagonists as visceral analgesics.

EP-A-279512 (Beecham Group p.l.c.) describes the use of certain 5-HT_3 receptor antagonists, including granisetron (KYTRIL) in the treatment of visceral pain.

Visceral pain is a symptom of irritable bowel syndrome (IBS) and granisetron has been found to desensitise the rectum in IBS patients as shown by double-blind placebo-controlled studies, at doses of 120 µg/kg and 50 µg/kg, 120 µg/kg being most effective. (Prior and Read, 1990; Gut 31 (10) A1174).

Granisetron has been found to be active in an animal model of rectal sensitivity to distension (see method described hereafter).

5-HT_3 receptor antagonists which have the same effect as granisetron in this model, include zatosetron (Lilly) and metoclopramide.

The invention therefore relates to the use of those 5-HT_3 receptor antagonists, which are active in the animal model at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also migraine.

Preferred compounds are active at a lower dose than the 5-HT_3 receptor antagonist dose. Compounds which are approved or under clinical investigation are active at a similar dosage level to that which is used for antiemetic use.

Suitable modes of administration, formulations, etc. are as described in EP-A-279512.

5-HT_3 receptor antagonists which should be considered for this invention include those specifically and generically disclosed and referenced in EP-A-450757 (Glaxo Group Limited).

Rat Model of Colo-rectal Distension

A 6-7 cm latex balloon was inserted intra-anally into male Wistar rats (250-650g) under halothane anaesthesia; the balloon catheter was taped to the tail. After recovery the animals were allowed unrestricted movement and were dosed with either vehicle (saline) or 5-hydroxytryptophan (5-HTP 10mgkg^{-1} subcutaneously). At 5 min post-dose a ramp inflation of the colo-rectal balloon was carried out for approximately 10-30s until the visceromotor threshold (abdominal muscle contraction) was observed; the stimulus was then immediately removed and threshold pressure noted. This inflation procedure was repeated at 5 min intervals. 5-HT_3 receptor antagonists or saline were dosed subcutaneously after 3 stable responses were achieved and within 45 min of dosing 5-HTP or vehicle. The visceromotor threshold values were then recorded for a further 30 min. A similar model was described by Ness & Gebhart (1988, Brain Res. 450, 153-169). Maximum percentage changes (within the 30 min post-dose period) in distension pressure were compared with the mean of the pre-dose recordings. Saline control values were then assigned the value of 1.00 and drug induced changes compared directly.

Saline vehicle had no effect on the visceromotor threshold, whilst the dose of 5-HTP caused a reduction in the distension pressure required to elicit a response to the noxious stimulus (mean reduction of 30.7 $\pm$ 4.4%). Thus, by using a dose of 5-HTP that did not cause dramatic increases in gut secretion, the rat colo-rectum could be sensitised to colo-rectal distension.

Addition of saline after a pre-dose of 5-HTP had no effect on the decrease in threshold pressure caused by 5-HTP. By comparison, it was found that some, BUT NOT ALL, 5-HT_3 receptor antagonists when administered after 5-HTP dose dependently raised the visceromotor threshold above pre-dose values, thereby displaying a reduction in the sensitivity of the sensitized colo-rectum and producing analgesia to noxious levels of visceral distension. The Table shows the differences between selected 5-HT_3 receptor antagonists. Note that those antagonists that are active as visceral analgesics all display bell-shaped dose effect curves.

COMPOUND	DOSE	INDEX	SEM
	$\mu g/kg^{-1}$		
saline	-	1.00	0.27
5-HTP	10 000	-1.63	0.23
granisetron	1	2.17	0.40
	10	4.18	0.59
	100	2.86	0.66
	1000	2.17	0.37
	10 000	2.00	0.69
tropisetron	10	1.31	0.33
	100	1.77	0.73
metoclopramide	1	1.88	0.35
	10	2.69	0.43
	100	2.15	0.65
BRL 46470	1	0.46	0.38
	10	1.50	0.32
	100	0.02	0.28
	1000	0.55	0.39
E5*	1	2.54	0.87
	10	4.31	0.60
	100	1.79	0.56
ondansetron	10	1.03	0.15
	100	0.94	0.20
	1000	0.44	0.24
	10 000	1.61	0.49
zatosetron	1	2.73	0.77
	10	3.55	0.44
	100	2.66	0.55

*Example 5 of EP-A-377967

Thus it can be seen that granisetron, E5 and zatosetron are visceral analgesics (increasing threshold values above control by > 4-fold) falling within the invention.

Intrathecal administration of granisetron (100mg) also showed good analgesic activity suggesting that a site of action, of those 5-HT_3 receptor antagonists that are visceral analgesics, may be in the spinal cord. Furthermore, recent evidence from neonatally capsaicin treated rats, where there is c-fibre deafferentation, suggests the presence of these 5-HT_3 receptors on primary afferent fibres or a role for these receptors in sensory processing mediated by capsaicin sensitive afferents.

Claims

1. A method for the treatment and/or prophylaxis of visceral pain, in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT_3 receptor antagonist, which is active in the animal model at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model.

2. The use of those 5-HT_3 receptor antagonists, which are active in the animal model at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain.

3. A pharmaceutical composition for use in the treatment and/or prophylaxis of visceral pain, which comprises a 5-HT_3 receptor antagonist, which is active in the animal model at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, and a pharmaceutically acceptable carrier.

4. A method, use or composition according to claim 1, 2 or 3 wherein the compound is active at a lower dose than the 5-HT_3 receptor antagonist dose.

5. A method, use or composition according to claim 4 for the treatment of the pain symptoms of IBS.

6. A method, use or composition according to claim 5 for the treatment of also migraine.

7. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT_3 receptor antagonist is selected from those specifically and generically disclosed and referenced in EP-A-450757 (Glaxo Group Limited).

8. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT_3 receptor antagonist is granisetron.

9. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT_3 receptor antagonist is zatosetron (Lilly) or metoclopramide.